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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
11/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/541,894	KLOKKERS ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-30,32,33 and 35-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-30,32,33 and 35-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 06/29/09 are acknowledged.

2. Claims 1-23, 31 and 34 were cancelled. Claims 24, 32-33, 41 and 46 were amended.

3. Claims 24-30, 32-33, and 35-48 are included in the prosecution.

Response to Arguments

Rejection of claim 24 under 35 USC § 112, 2nd paragraph

4. Applicant's arguments, see Page 7, filed 06/29/09, with respect to the rejection of claim 24 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention, have been fully considered and are persuasive in light of the amendment of claim 24 to include the terms "comprising caprylic and capric acid triglycerides." Therefore, the rejection of 03/30/09 has been withdrawn.

Rejection of claims 24-31, 35, 38, 40-43 and 45-48 under 35 USC § 102(b)

5. Applicant's arguments, see Page 9, filed 06/29/09, with respect to the rejection of claims 24-31, 35, 38, 40-43 and 45-48 under 35 U.S.C. 102(b) as being anticipated by Price et al. (US 4,128,658), have been fully considered and are persuasive in light of the amendments of claims 24, 41 and 46 to include the terms "comprising caprylic and capric acid triglycerides." Therefore, the rejection of 03/30/09 has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made under 35 U.S.C. 103(a) over Price et al. (US 4,128,658) in view of Fuisz (US 5,387,431).

Rejection of claims 24-25, 28-30, 35-36, and 45-47 under 35 USC § 102(b)

6. Applicant's arguments, see Page 10, filed 06/29/09, with respect to the rejection of claims 24-25, 28-30, 35-36, and 45-47 under 35 U.S.C. 102(b) as being anticipated by Fuisz (US 5,387,431), have been fully considered and are persuasive in light of the amendments of claims 24 and 46 to include the terms "comprising caprylic and capric acid triglycerides." Therefore, the rejection of 03/30/09 has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made under 35 U.S.C. 103(a) over Price et al. (US 4,128,658) in view of Fuisz (US 5,387,431).

Rejection of claims 32-33, 36-37, 39 and 44 under 35 USC § 103(a)

7. Applicant's arguments, see Page 11, filed 06/29/09, with respect to the rejection of claims 32-33, 36-37, 39 and 44 under 35 U.S.C. 103(a) as being unpatentable over Price et al. (US 4,128,658) in view of Santus et al. (US 5,472,704), have been fully considered and are persuasive in light of the amendments of claims 24, 32-33 and 41. Therefore, the rejection of 03/30/09 has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made under 35 U.S.C. 103(a) over Price et al. (US 4,128,658) in view of Fuisz (US 5,387,431) and further in view of Santus et al. (US 5,472,704).

NEW REJECTIONS:

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 24-30, 35, 38, 40-43, and 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (US 4,128,658) in view of Fuisz (US 5,387,431).

The claimed invention is a method for preparing granules for a pharmaceutical formulation comprising wetting a mixture of one or more active ingredients and one or more lipophilic retarding agents with an oily substance selected from the group consisting of neutral oil comprising caprylic and capric acid triglycerides, sesame oil, peanut oil, olive oil, almond oil, soybean oil, coconut oil, cottonseed oil, corn oil, rape oil, sunflower oil, wheat kernel oil, liquid paraffin, wax solutions in organic oil, and low viscosity wax; and granulating the wetted mixture so that granules for a pharmaceutical formulation are prepared.

Price teaches a method of producing oral sustained release tablets. "The active ingredient, anhydrous lactose and most of the Cutina HR (a hydrogenated castor oil) are intimately mixed and then the mixture is moistened by mixing with a 10% solution of the remainder of the Cutina HR ... the moistened mass is granulated through a 1.2 mm aperture sieve and dried at 50ºC in a fludised bed dryer. The granules are then passed through a 0.85 mm aperture sieve, blended with the magnesium stearate and compressed ... on a tableting machine with 12.5mm diameter punches" (Col. 29, Example c, lines 29-47). In another exemplified preparation (for an oral syrup), the drug is dissolved in water (Col. 29, line 56). Since the drug dissolves in water it is hydrophilic.

Price does not expressly teach an oily substance selected from the group consisting of neutral oil comprising caprylic and capric acid triglycerides, sesame oil,

peanut oil, olive oil, almond oil, soybean oil, coconut oil, cottonseed oil, corn oil, rape oil, sunflower oil, wheat kernel oil, liquid paraffin, wax solutions in organic oil, and low viscosity wax.

Fuisz teaches a method of preparing a substantially solid saccharide-based matrix comprising subjecting a feedstock comprising a mixture of solid maltodextrin and an oleaginous material to conditions of force and temperature (Col. 25, claim 6). The process can be used to prepare pharmaceutical materials and suitable active ingredients, including vitamins and acetaminophen (water soluble actives) are disclosed (Col. 6, line 53 to Col. 7, line 41). Example 16 discloses the preparation of a pharmaceutical containing sucralfate, xanthan gum, corn oil and maltodextrins, including mixing the materials and processing in order to produce a particulate product (Col. 15, lines 14-20).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of producing granules by mixing an active ingredient, a portion of a lipophilic retarding agent (hydrogenated castor oil) and subsequently mixing with the remainder of the hydrogenated castor oil, as suggested by Price, substitute the hydrogenated castor oil with the corn oil used in a mixture of active ingredient and excipients, as suggested by Fuisz, and produce the instant invention.

One of ordinary skill in the art would have been motivated to substitute the remainder of hydrogenated castor oil (taught by Price) with corn oil (taught by Fuisz) because simple substitution of one known element for another to obtain predictable results is obvious. Please see MPEP 2141. Both references teach the mixing of active

ingredients with lipophilic retarding materials and oily substances. Therefore, substituting one oily substance for another would have been obvious. One of ordinary skill in the art would have a reasonable expectation of success in producing a functional granulate comprising active ingredient and a lipophilic retarding agent.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claims 24 and 41, the limitations of a method for preparing granules comprising wetting a mixture of one or more active ingredients and one or more retarding agents would have been obvious over the granulation method of an active ingredient mixed with anhydrous lactose and a hydrogenated castor oil taught by Price (Col. 29, Example c, lines 29-47). The lipophilic retarding agent is the lipophilic hydrogenated castor oil. The instant specification (Page 9, 1st paragraph) discloses that "suitable lipophilic retarding agents (= fat matrix-forming agents) are, for example ... hydrogenated vegetable oils, such as hydrogenated castor oil (Cutina HR) ..." The limitation of mixing the active ingredient and the lipophilic retarding agent with an oily substance (selected from the group consisting of neutral oil comprising caprylic and capric acid triglycerides, sesame oil, peanut oil, olive oil, almond oil, soybean oil, coconut oil, cottonseed oil, **corn oil**, rape oil, sunflower oil, wheat kernel oil, liquid paraffin, wax solutions in organic oil, and low viscosity wax) would have been obvious

over the moistening of the intimate mixture of the active ingredient, anhydrous lactose and the hydrogenated castor oil by the remainder of the hydrogenated castor oil, as taught by Price (Col. 29, Example c, lines 29-47) in view of mixing a drug (sucralfate), xanthan gum, and maltodextrin with **corn oil**, as taught by Fuisz (Col. 15, lines 14-20). One of ordinary skill in the art would find it obvious to substitute the remainder of the hydrogenated castor oil used for moistening (or wetting) the mixture of active ingredient and lipophilic retarding agent (also hydrogenated castor oil) that is taught by Price with the corn oil that is used in the mixture of active ingredient and oleaginous material, as taught by Fuisz, with a reasonable expectation of success in producing a functional granule comprising a mixture of an active ingredient, a lipophilic retarding agent, and an oily substance. The granulation step would have been obvious over the fluidized bed granulation step taught by Price (Col. 29, Example c, lines 29-47). The limitation of compressing the granules so that tablets are prepared of instant claim 41 would have been obvious over the compression of granules to form tablets as taught by Price (Col. 29, Example c, lines 29-47). The limitation of the oily substance would have been obvious over the CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47) in view of the corn oil taught by Fuisz (Col. 15, lines 14-20).

Regarding instant claim 25, the limitation of the mixture further comprising excipients would have been obvious over the excipient anhydrous lactose taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 26, the limitation of wetting the mixture by spraying would have been obvious over the fluidized bed spray dryer taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 27, the limitation of wetting the mixture at room temperature would have been obvious over the method taught by Price (Col. 29, Example c, lines 29-47). Since Price does not disclose a specific temperature for the wetting or moistening step, one skilled in the art can readily envisage that the process is carried out at room temperature.

Regarding instant claim 28, the limitation of a hydrophilic active ingredient would have been obvious over the active ingredient that dissolves in water, as taught by Price (Col. 29, line 56). Since the drug dissolves in water it is inherently hydrophilic.

Regarding instant claims 29-30, the limitation of the active ingredient content would have been obvious over the 37.5% (1.5Kg/4Kg) of active ingredient as taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 35, the limitations of the percentage of the oily substance would have been obvious over the 10% (0.4Kg/4Kg) of CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 38, the limitation of the fluidized bed granulator would have been obvious over the fludised bed dryer taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 40, the limitation of compressing the granules into tablets would have been obvious over the tablets formed by compressing granules as taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 42, the limitation of mixing the granules with at least one excipient prior to compressing the granules would have been obvious over mixing magnesium stearate with the granules before compressing into tablets as taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 43, the limitation of the excipient would have been obvious over the lubricant magnesium stearate taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claims 45-48, the limitations of the granules and the tablet would have been obvious over the granules and tablet prepared by the method taught by Price (Col. 29, Example c, lines 29-47). The limitation of the oily substance would have been obvious over the CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47) in view of the corn oil taught by Fuisz (Col. 15, lines 14-20).

10. Claims 32-33, 36-37, 39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Price et al. (US 4,128,658) in view of Fuisz (US 5,387,431) and further in view of Santus et al. (US 5,472,704).

The teachings of Price and Fuisz are stated above.

Price and Fuisz do not expressly teach the combination of the lipophilic retarding agent with a hydrogel matrix forming agent or a structural matrix forming agent.

Santus teaches bioadhesive granules with matrix units for the controlled release of furosemide (Col. 8, lines 63-64, Example 1). A hydrophobic matrix is obtained by granulation with melted excipients (Col. 8, lines 66-67). "50 parts of furosemide are mixed with 25 parts of hydrogenated castor oil and the resulting mixture is kneaded using 25 parts of melted hydrogenated castor oil as a granulation fluid. The resulting mixture is granulated ... the granules are mixed with ... an acrylic copolymer and ... hydroxypropylmethylcellulose ... the mixture is then tableted in an eccentric press ... obtaining tablets with a diameter of 21mm. The tablets are then crumbled and sieved so as to obtain granules ..." (Col. 9, lines 1-12). A fluid bed system (WURBTER-GLATT®) is disclosed (Col. 8, lines 58-59). Excipients that are commonly known in the art are disclosed (Col. 7, lines 1-5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of producing granules by mixing an active ingredient, a portion of a lipophilic retarding agent (hydrogenated castor oil) and subsequently mixing with the remainder of the hydrogenated castor oil, as suggested by Price, substitute the hydrogenated castor oil with the corn oil used in a mixture of active ingredient and excipients, as suggested by Fuisz, further combine it with the method of producing granules of active ingredients with a lipophilic retarding agent in combination with acrylic copolymer and hydroxypropylmethylcellulose, as taught by Santus, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Santus teaches that cellulose derivatives such as hydroxypropylmethylcellulose

(HPMC) are bioadhesive polymers. One of ordinary skill in the art would know that bioadhesive polymers are crucial for extended release formulations and would include it for extending the release of hydrophilic active ingredients.

Regarding instant claims 32-33, the limitations of the structural matrix forming agent and hydrogel matrix forming agent would have been obvious over the HPMC taught by Santus (Col. 9, lines 1-12). The limitation of the water soluble excipients would have been obvious over the anhydrous lactose taught by Price (Col. 29, Example c, lines 29-47).

Regarding instant claim 36, the percentage range of the oily substance would have been obvious over the 10% (0.4Kg/4Kg) of CUTINA HR® (hydrogenated castor oil) taught by Price (Col. 29, Example c, lines 29-47). One of ordinary skill in the art would modify the level of the oily substance during the process of routine experimentation in order to optimize the sustained or extended release attributes and the stability of the resultant granules.

Regarding instant claim 37, the limitation of the granules further comprising an outer phase of one or more retarding agents would have been obvious over the microunit coating taught by Santus. The method disclosed can coat individual microunits (Col. 8, lines 36-40).

Regarding instant claim 39, the limitation of the granule binder would have been obvious over the HPMC taught by Santus (Col. 9, lines 1-12).

Regarding instant claim 44, the limitation of the tablet further comprising a coating would have been obvious over the tablets taught by Price (Col. 29, Example c,

lines 29-47) and because one of ordinary skill in the art would employ tablet coatings during the process of routine optimization in order to enhance the stability and shelf-life of the tablet, to mask the off-notes, and to provide a layer of sustained release coating for extending the therapeutic effect of the chosen active ingredient.

Conclusion

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached at 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/Robert A. Wax/
Supervisory Patent Examiner, Art Unit 1615